Tetrahedron Letters xxx (2015) xxx–xxx

Contents lists available at ScienceDirect

Tetrahedron Letters

journal homepage: www.elsevier.com/locate/tetlet

Nonstabilized azomethine ylides as reagents for alkylaminomethylation of aromatic ketones via 5-aryloxazolidines

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ARTICLE INFO

Article history:
Received 1 June 2015
Revised 15 July 2015
Accepted 22 July 2015
Available online xxxx

Keywords:
Carbonyl compounds
Nonstabilized azomethine ylides
[3+2] Cycloaddition
5-Aryloxazolidines
2-Amino-1-arylethanols

ABSTRACT

Aromatic ketones were found to react smoothly with nonstabilized azomethine ylides, generated in situ from sarcosine/formaldehyde or *N*-(methoxymethyl)-*N*-(trimethylsilylmethyl)benzylamine, to give 5-aryloxazolidines which were converted into 2-alkylaminoethanols in moderate to good yields by heating in *n*-butanol with hydrochloric acid.

The 2-amino-1-arylethanol functional group is a structural unit found in a large number of natural products and bioactive compounds such as peptide enzyme inhibitors, amino sugar antibiotics, alkaloids, and sympathomimetic amines.[1] Examples of such compounds include the alkaloids halostachine, longimammine, and normacromerine,[2] as well as the drugs phenylephrine and epinephrine.[3] Diarylaminoethanols and their desoxy derivatives have also drawn considerable attention because of their unique biological and physiological activities.[4,5] Moreover, 2-amino-1-arylethanols are also employed for the preparation of chiral auxiliaries,[6] and are important precursors in several synthetic drugs and natural products.[7]

The introduction of the aminomethyl fragments to electrophilic compounds such as aromatic aldehydes and ketones is widespread in synthetic organic chemistry. Typically, this is achieved by cyanohydrin synthesis[6,8] or the Henry reaction of nitromethane, followed by hydrogenation to the desired 2-amino-1-arylethanols.[9] The insertion of a more complex alkylaminomethyl anion synthon **I** based on the above strategies requires multiple steps, including N-alkylation of the primary amines.[10] Finally, 2-aryloxiranes can be synthesized from the corresponding carbonyls and ring-opened with nitrogen nucleophiles.[11]

From another point of view, synthetic equivalents of the alkylaminomethyl anion **I** would possess certain advantages if they could be directly introduced to keto compounds. The requirements for such molecules would firstly be an absence of an acidic NH proton and secondly stabilization of the negative charge on the carbon atom. Among the more common methylaminomethyl anion precursors are *O*-*tert*-butyl-*N*-(chloromethyl)-*N*-methyl carbamate[12] and *N*,*N*-dimethylthiopivalamide.[13] These compounds are lithiated at the Me group in an α-position to the nitrogen atom using an excess of lithium powder or *s*-BuLi to generate the methylaminomethyl anion equivalents **II** and **III** which are then reacted with an electrophile, followed by removal of the Li-coordinating moiety attached to nitrogen. Such reactions are limited by the complex conditions required for the initial deprotonation and final hydrolysis steps. Therefore, these precursors have not found widespread application due to the difficulties in their preparation and utilization. On the other hand, synthetic equivalents of such types are 2-azaallyl anion **IV** which can be generated from *N*-(trimethylsilylmethyl)imines,[14] and nonstabilized azomethine ylide **V**. The latter example is highly reactive and easily accessible, which makes it very attractive (Scheme 1).

A novel azomethine ylide strategy for the introduction of the alkylaminomethyl group to aromatic aldehydes has been recently developed by our research group.[15] This approach, based on the 1,3-dipolar cycloaddition of nonstabilized azomethine ylides with a carbonyl functional group, represents one of the simplest conversions of carbonyl compounds into 2-amino-1-arylethanols and it was felt that further investigations in order to expand the scope of its possible applications were required. Taking into account the broad utility of 2-amino alcohols in medicinal chemistry and continuing our research in the field of 5-aryloxazolidine chemistry,[16] we herein report our extension of this methodology to a number

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http://dx.doi.org/10.1016/j.tetlet.2015.07.068
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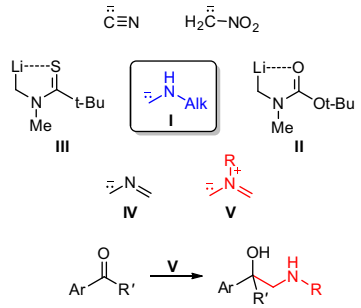
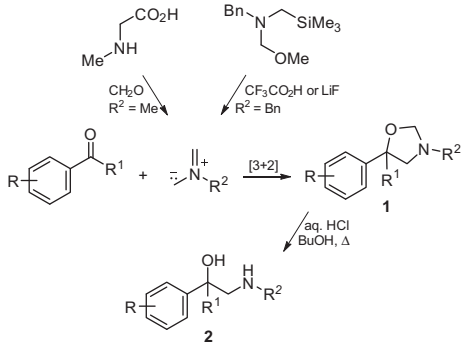


Scheme 1. Synthetic equivalents for the alkylaminomethyl anion.

of aromatic ketones and 1,2-diketones for the preparation of new 1,1-disubstituted 2-alkylaminoethanols.

Nonstabilized azomethine ylides have high nucleophilicity and can be readily generated from *N*-alkyl-α-amino acids or *N*-(methoxymethyl)-*N*-(trimethylsilylmethyl)benzylamine (Scheme 2). However, in contrast to the well documented reactivity of the C=C double bond, to date little attention has been paid to the [3+2] cycloaddition reaction of carbonyl compounds with nonstabilized azomethine ylides. The pioneering studies of Rizzi,[17] Padwa,[18] Orsini,[19] and Nyerges[20] established that nonstabilized azomethine ylide [3+2] cycloadditions with carbonyl compounds enable a one-step synthesis of 5-aryloxazolidines. Although several papers regarding their preparation have been published,[21] the synthetic utility of these intermediates has not been extensively explored. Only three papers describing intra- and intermolecular reactions of 5-aryloxazolidines with nucleophilic reagents have been reported.[16a–c] In view of the fact that the aminoacetal methylene group of 5-aryloxazolidines **1**, the former azomethine ylide cationic center, retains electrophilic character after the cycloaddition step due to the presence of the two geminal acceptor atoms, we envisaged that the ring-opening of the oxazolidines by removing the methylene group would produce the corresponding 2-amino-1-arylethanols **2**, providing a general and simple route for the synthesis of these valuable compounds (Scheme 2). It is noteworthy that a similar introduction of more complex amino acid fragments to aldehydes has been previously achieved using stabilized azomethine ylides.[22]

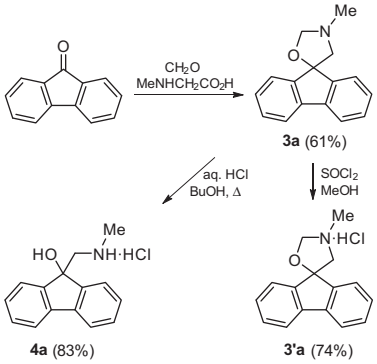
Initially, we investigated the reaction of sarcosine and paraformaldehyde with aromatic ketones. In previous publications using coumarins and chromones we observed that nonstabilized azomethine ylides reacted poorly with weak electron-withdrawing or sterically hindered dipolarophiles.[16e,23] We envisaged that the reactions with more active fluorenone and (trifluoromethyl)phenylketone may produce the corresponding oxazolidines in good yield.



Scheme 2. Synthesis of β-hydroxy-β-phenethylamines **2**.

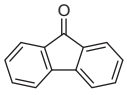
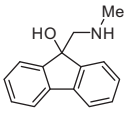
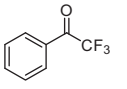
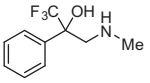
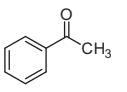
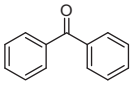
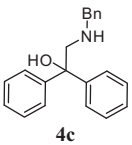
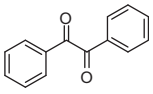
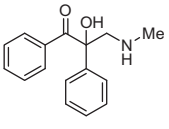
Indeed, we found that the reaction with fluorenone led to previously unknown oxazolidine **3a** in 96% NMR yield, which could be readily purified by recrystallization in 61% yield. Utilization of the typical ring-opening procedure ($HCl/H_2O/MeOH$)[15] on this oxazolidine did not proceed to completion, however use of the higher boiling *n*-BuOH at 90 °C for 1.5 h gave hydrochloride **4a** in 83% yield. Attempts to demethylenate oxazolidine **3a** by refluxing with dry HCl (from $SOCl_2$) in MeOH gave only the hydrochloride of the starting compound **3′a**. The latter observation can be accounted for by the fact that such aminoalcohols are only formed in the presence of water (Scheme 3, Table 1, entry 1).

As expected, (trifluoromethyl)phenylketone reacted readily with the azomethine ylide derived from sarcosine and formaldehyde to give liquid oxazolidine **3b**, which, without isolation, was hydrolyzed to give the hydrochloride salt of 2-amino alcohol **4b** in 70% yield (Table 1, entry 2). Thus, the described one-pot synthesis of 2-methylamino-1-arylethanols from aromatic ketones



Scheme 3. Synthesis of compounds **3a** and **4a**.

Table 1
Yields of hydrochlorides **4**

Entry	Aromatic ketone	NMR yield of oxazolidine **3**[a] (%)	2-Aminoethanol **4**·HCl	Isolated yield of **4**·HCl[b] (%)
1		96 (61)[c]	 **4a**	83
2		Quant.	 **4b**	70
3		64%[d]	—[e]	—
4		72	 **4c**	34
5		Quant.	 **4d**	86